Application No.: 10/540,304

Office Action Dated: December 31, 2007

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Currently Amended) A compound according to the general Formula (I)

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the N-oxide form thereof <u>or and</u> prodrugs thereof, wherein:

n is an integer, equal to 0, 1 or 2;

m is an integer, equal to 1-or 2, provided that if m is 2, then n is 1;

p is an integer equal to 1 or 2;

q is an integer equal to 0 or 1;

Q is O or NR^3 -;

X is a covalent bond or a bivalent radical of formula O, S or NR³-;

each R³—independently from each other, is hydrogen or alkyl;

each R¹ independently from each other, is independently selected from the group of Ar¹[[,]]or Ar¹-alkyl and di(Ar¹) alkyl;

R² is Ar², Ar² alkyl, di(Ar²)alkyl, Het⁴ or Het⁴ alkyl;

Y is a covalent bond or a bivalent radical of formula $-C(=O)-[[,]]or -SO_2-$; >C=CH R or >C=N R, wherein R is CN or nitro;

- each Alk <u>isrepresents</u>, independently from each other, a covalent bond; a bivalent straight or branched, saturated or unsaturated-hydrocarbon radical having from 1 to 6 carbon atoms; or a cyclic saturated or unsaturated hydrocarbon radical having from 3 to 6 carbon atoms; each radical optionally substituted on one or more carbon atoms with one or more alkyl, phenyl, halo, cyano, hydroxy, formyl and amino radicals;
- L is selected from the group of hydrogen, alkyl, alkyloxy, Ar³-oxy, alkyloxycarbonyl, alkylcarbonyloxy, mono- and di(alkyl)amino, mono- and di(Ar³)amino, mono- or and di(alkyloxycarbonyl)amino, Ar³, Ar³carbonyl, or Page 9 of 17

PATENT

DOCKET NO.: JANS-0076/JAB1730F

Application No.: 10/540,304

Office Action Dated: December 31, 2007

Het² and Het² carbonyl;

Ar¹ is phenyl, optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, alkyl, cyano, aminocarbonyl and alkyloxy;

- Ar² is naphtalenyl or phenyl, each optionally substituted with 1, 2 or 3 <u>alkyl</u> substituents, each independently from each other, selected from the group of halo, nitro, amino, mono—and di(alkyl)amino, cyano, alkyl, hydroxy, alkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl and mono—and di(alkyl)aminocarbonyl;
- Ar³ is naphthalenyl or phenyl, optionally substituted with 1[[,]] or 2-or 3 substituents, each independently from each other, selected from the group of alkyloxy, alkyl, halo, hydroxy, pyridinyl, morpholinyl, pyrrolidinyl, imidazo[1,2 a]pyridinyl, morpholinylcarbonyl, pyrrolidinylcarbonyl, amino and or cyano;
- Het¹ is a monocyclic heterocyclic radical selected from the the group of pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocyclic radical selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl; each heterocyclic radical may optionally be substituted on any atom by a radical selected from the group of halo and alkyl;

Het² is a monocyclic heterocyclic radical that is selected from the group of pyrrolidinyl, dioxolyl, imidazolidinyl, pyrrazolidinyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, imidazolidinyl, tetrahydrofuranyl, 2H-pyrrolyl, pyrrolinyl, imidazolinyl, pyrrazolinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, pyridinyl[[,]] or pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl; or a bicyclic heterocyclic radical selected from the group of benzopiperidinyl, quinolinyl, quinoxalinyl, indolyl, isoindolyl, chromenyl, benzimidazolyl, imidazo[1,2 a]pyridinyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzothiazolyl, benzothiazolyl, benzothiazolyl, benzothiazolyl, benzofuranyl and benzothienyl;

each radical optionally substituted with one or more <u>alkyl or alkyloxycarbonyl</u> radicals selected from the group of Ar¹, Ar¹alkyl, halo, hydroxy, alkyl, piperidinyl, pyrrolyl, thienyl, oxo, alkyloxy, alkyloxyalkyl and <u>alkyloxycarbonyl</u>; and

DOCKET NO.: JANS-0076/JAB1730F

Application No.: 10/540,304

Office Action Dated: December 31, 2007

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radicals having from 3 to 6 carbon atoms; optionally substituted on one or more carbon atoms with one or more radicals selected from the group of phenyl, halo, cyano, oxo, hydroxy, formyl and amino.

2. (Cancelled) A compound according to claim 1, characterized in that

n is 1;

m = is 1;

p is 1;

 $\frac{1}{q}$ is 0;

Q = is O;

X is a covalent bond;

each R⁴ is Ar⁴ or Ar⁴ alkyl;

 $R^2 = is Ar^2$;

Y is a covalent bond or a bivalent radical of formula C(=O) or SO₂;

each Alk represents, independently from each other, a covalent bond; a bivalent straight saturated hydrocarbon radical having from 1 to 6 carbon atoms; each radical optionally substituted on one or more carbon atoms with one or more phenyl radicals;

L is selected from the group of hydrogen, alkyl, mono and di(alkyloxycarbonyl)amino, Ar^3 and Het^2 ;

 Ar^4 is phenyl;

Ar² is phenyl, each optionally substituted with 1,2 or 3 alkyl substituents;

Ar³ is phenyl, optionally substituted with 1 or 2 substituents, each independently from each other selected from the group of halo and cyano;

Het² is a monocyclic heterocyclic radical selected from the group of tetrahydrofuranyl, pyrrolidinyl, pyrazolyl, furanyl, thienyl, pyrimidinyl, thiadiazolyl and pyridinyl; each radical optionally substituted with one or more alkyl or alkyloxycarbonyl radicals; and

alkyl is a straight saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radicals having from 3 to 6 carbon atoms.

3. (Previously Presented) A compound according to claim 1 wherein R^1 is Ar^1 methyl and attached to the 2-position or R^1 is Ar^1 and attached to the 3-position.

DOCKET NO.: JANS-0076/JAB1730F

Application No.: 10/540,304

Office Action Dated: December 31, 2007

- 4. (Previously Presented) A compound according to claim 1 wherein the R²-X-C(=Q)- moiety is 3,5-di-(trifluoromethyl) phenylcarbonyl.
- 5. (Canceled) A compound according to claim 1 wherein p is 1.
- 6. (Previously Presented) A compound according to claim 1 wherein Y is -C(=O)-.
- 7. (Previously Presented) A compound according to claim 1 wherein Alk is a covalent bond.
- 8. (Previously Presented) A compound according to claim 1 wherein L is Het².
- 9. (Currently Amended) A compound that is selected from the group of compounds with compound number 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 and 22 as described in Table 1.
 - (2R-trans) [4-(4-azetidin-3-yl-piperazin-1-yl)-2-benzyl-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone;
 - $\frac{(2R-trans)\{4-[4-(1-benzoyl-azetidin-3-yl)-piperazin-1-yl]-2-benzyl-piperidin-1-yl\}-}{(3,5-bis-trifluoromethyl-phenyl)-methanone;}$
 - (2R-trans)3-(3-{4-[2-benzyl-1-(3,5-bis-trifluoromethyl-benzoyl)-piperidin-4-yl]-piperazin-1-yl}-azetidine-1-carbonyl)-benzonitrile;
 - (2R-trans) (2-benzyl-4-{4-[1-(3,4-difluoro-benzoyl)-azetidin-3-yl]-piperazin-1-yl}-piperidin-1-yl)-(3,5-bis-trifluoromethyl-phenyl)-methanone;
 - (2R-trans) (2-benzyl-4-{4-[1-(pyridine-3-carbonyl)-azetidin-3-yl]-piperazin-1-yl}-piperidin-1-yl)-(3,5-bis-trifluoromethyl-phenyl)-methanone;
 - (2R-trans) (2-benzyl-4-{4-[1-(2,5-dimethyl-2*H*-pyrazole-3-carbonyl)-azetidin-3-yl]-piperazin-1-yl}-piperidin-1-yl)-(3,5-bis-trifluoromethyl-phenyl)-methanone;
 - $\underline{(2R-trans)\ (2-benzyl-4-\{4-[1-(thiophene-3-carbonyl)-azetidin-3-yl]-piperazin-1-yl\}-piperidin-1-yl)-(3,5-bis-trifluoromethyl-phenyl)-methanone;}$
 - (2R-trans) (2-benzyl-4-{4-[1-(furan-3-carbonyl)-azetidin-3-yl]-piperazin-1-yl}-piperidin-1-yl)-(3,5-bis-trifluoromethyl-phenyl)-methanone;
 - (2R-trans) {2-benzyl-4-[4-(1-cyclopropanecarbonyl-azetidin-3-yl)-piperazin-1-yl]-piperidin-1-yl}-(3,5-bis-trifluoromethyl-phenyl)-methanone;

DOCKET NO.: JANS-0076/JAB1730F

Application No.: 10/540,304

Office Action Dated: December 31, 2007

- (2R-trans) (2-benzyl-4-{4-[1-((3R) tetrahydro-furan-3-carbonyl)-azetidin-3-yl]-piperazin-1-yl}-piperidin-1-yl)-(3,5-bis-trifluoromethyl-phenyl)-methanone;
- (2R-trans) (2-benzyl-4-{4-[1-((3S) tetrahydro-furan-3-carbonyl)-azetidin-3-yl]-piperazin-1-yl}-piperidin-1-yl)-(3,5-bis-trifluoromethyl-phenyl)-methanone;
- (2R-trans) [2-(3-{4-[2-benzyl-1-(3,5-bis-trifluoromethyl-benzoyl)-piperidin-4-yl]-piperazin-1-yl}-azetidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-carbamic acid *tert*-butyl ester;
- (2R-trans) 1-(3-{4-[2-benzyl-1-(3,5-bis-trifluoromethyl-benzoyl)-piperidin-4-yl]-piperazin-1-yl}-azetidin-1-yl)-2-phenyl-propan-1-one;
- (2R-trans) (2-benzyl-4-{4-[1-(thiophene-2-sulfonyl)-azetidin-3-yl]-piperazin-1-yl}-piperidin-1-yl)-(3,5-bis-trifluoromethyl-phenyl)-methanone;
- (2R-trans) (2-benzyl-4-{4-[1-(4-methyl-[1,2,3]thiadiazole-5-carbonyl)-azetidin-3-yl]-piperazin-1-yl}-piperidin-1-yl}-(3,5-bis-trifluoromethyl-phenyl)-methanone;
- (2R-trans)1-(3-{4-[2-benzyl-1-(3,5-bis-trifluoromethyl-benzoyl)-piperidin-4-yl]-piperazin-1-yl}-azetidin-1-yl)-2,2-dimethyl-propan-1-one;
- (2R-trans) (2-benzyl-4-{4-[1-(2-chloro-benzoyl)-azetidin-3-yl]-piperazin-1-yl}-piperidin-1-yl)-(3,5-bis-trifluoromethyl-phenyl)-methanone;
- (2R-trans) {2-benzyl-4-[4-(1-pyrazin-2-yl-azetidin-3-yl)-piperazin-1-yl]-piperidin-1-yl}-(3,5-bis-trifluoromethyl-phenyl)-methanone;
- (2R-trans) (2-benzyl-4-{4-[1-(pyrazine-2-carbonyl)-azetidin-3-yl]-piperazin-1-yl}-piperidin-1-yl)-(3,5-bis-trifluoromethyl-phenyl)-methanone;
- (2R-trans) 2-(3-{4-[2-benzyl-1-(3,5-bis-trifluoromethyl-benzoyl)-piperidin-4-yl]-piperazin-1-yl}-azetidine-1-carbonyl)- (2S) pyrrolidine-1-carboxylic acid *tert*-butyl ester.
- 10. (Canceled)
- 11. (Canceled)
- 12. (Currently Amended) A method for treating a patient suffering from The use of a compound according to claim 1 for treating-schizophrenia, emesis, anxiety, depression, irritable bowel syndrome (IBS), circadian rhythm disturbances, pain, neurogenic

PATENT

DOCKET NO.: JANS-0076/JAB1730F

Application No.: 10/540,304

Office Action Dated: December 31, 2007

inflammation, asthma, micturition disorders <u>or and</u> nociception, <u>comprising</u> <u>administering to the patient a therapeutically effective amount of a compound according</u> to claim 1.

- 13. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to claim 1.
- 14. (Previously Presented) A process for preparing a pharmaceutical composition comprising mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound of claim 1.
- 15. (Currently Amended) A process for the preparation of a compound of Formula (I") in which an intermediate compound of Formula (II) is reacted with an intermediate compound of Formula (III), wherein the radicals R², X, Q, R¹, m, n, p and q are as defined in claim 1.

wherein

X is a covalent bond;

each R¹ is independently Ar¹ or Ar¹-alkyl;

 R^2 is Ar^2 ;

n is an integer, equal to 1;

m is an integer, equal to 1;

p is an integer equal to 1;

q is an integer equal to 0; and

Q is O.

DOCKET NO.: JANS-0076/JAB1730F PATENT

Application No.: 10/540,304

Office Action Dated: December 31, 2007

16. (Original) A process for the preparation of a compound of Formula (I') in which a final compound of Formula (I") is reductively hydrogenated, wherein the radicals R², X, Q, R¹, m, n, p and q are as defined in claim 1.

wherein

X is a covalent bond;

each R¹ is independently Ar¹ or Ar¹-alkyl;

 R^2 is Ar^2

n is an integer, equal to 1;

m is an integer, equal to 1;

p is an integer equal to 1;

q is an integer equal to 0; and

Q is O.

- 17. (Original) A process for the preparation of a compound according to Formula (I') comprising the consecutive steps of
 - 1) obtaining a compound of Formula (I") according to claim 15 ;
 - 2) obtaining a compound of Formula (I') according to claim 16